

(US 5,558,879). Reconsideration and withdrawal of this rejection is respectfully requested based upon the following considerations.

The Present Invention and Its Advantages

The present invention provides for controlled release preparations having multi-layer structures. The preparations more particularly relate to controlled drug-release formulations having multi-layer structures, wherein one or more drugs can separately be released with a different behavior *in vivo*, for the purpose of exhibiting effectively the efficacy thereof.

In the present specification, experiments are carried out and reported between preparations of the present invention and comparative preparations. As seen upon reviewing Experiments 1-4 at pages 20-21 of the specification and Figures 2-5 referred to therein, the Examiner can easily see that the compositions of the present invention possess advantageous properties, and allow one to easily release one or more drugs separately with different behaviors *in vivo*.

Distinctions Over the Cited Art

In the Office Action, the USPTO asserts, in support of the rejection, that although Sano does not teach that the outer layer contains an active agent, it would have been obvious for a person of ordinary skill in the art to prepare a multiple layer

pharmaceutical composition of the present invention in view of Chen describing a formulation comprising an outer layer containing a medicament.

In reply to the USPTO's contention, Applicants submit that there is neither any suggestion nor motivation in either of the cited references to combine their disclosures in a fashion that might arguably arrive at the instant invention being claimed. In support of this contention, Applicants point to differences in (1) administration routes and the purposes of the formulations, and (2) the function and materials of the outer layers of the provided control release preparations.

Administration Routes and Purposes of the Formulations

Chen describes a tablet for oral administration, whereas Sano typically describes a formulation for intracorporeal implantation.

The formulation of Chen is designed to provide once a day dosing of a medicament, whereas the formulation of Sano is designed to provide a few months dosing of a medicament.

It is submitted that any combination of the teachings of Sano and Chen would require solving some problems, which are inherent to the respective technical fields and differences in formulations for oral administration versus intracorporeal implantation. Such differences would not motivate one skilled in

the art to combine the references' disclosures in a fashion that would arrive at the invention.

Function and Material of the Outer Layers

The differences in administration routes and purposes between the formulations of Chen and Sano results in part from differences in the functions of their respective outer layers.

The formulation of Chen essentially comprises a core and a dual layer comprising an inner layer and an outer layer. According to the medicament-releasing mechanism of Chen's formulation, a medicament comprised in the outer layer is first released, then an increase in the osmotic pressure inside the core, which is induced by water being taken up into the tablet, causes a small opening to form at the weakest point at an edge of the tablet, and, through the initial opening, the contents of the core are extruded by way of the increased osmotic pressure (see, col. 3, lines 41-46 of Chen et al.). Accordingly, the outer layer in Chen's formulation is designed to effect the initial medicament releasing in the mechanism as mentioned above, and specifically it is designed to release a medicament for at most 30 minutes from the initial point until the opening for extruding a medicament is formed. Further, when Figure 1 and Figure 2 of Chen are taken together, it is shown that the outer layer supplements the medicament release for the first 30 minutes in view of Figure 1 showing that the amount of

medicament that is released within the first one to two hours is poor.

On the other hand, the outer layer of the formulation of Sano is impermeable to water, and contributes to a limited channeling and cracking of inner layer(s), thus enabling a release of medicament for a long period of time (see, page 7, lines 18-27 of Sano et al.). Figures 3-6 of Sano show that the disclosed formulation releases a medicament for a period of up to a few months.

Further, the difference in function of the outer layers of Chen and Sano leads to a difference in the material of the respective outer layers.

The outer layer of Chen's formulation is prepared by dissolving a water soluble medicament in a water-soluble polymer (see, column 2, lines 24-27 of Chen et al.). Accordingly, once the formulation disclosed in Chen is orally administered, the outer layer of the formulation will dissolve in gastrointestinal fluid, and disappear immediately, with the assistance of gastrointestinal movements.

On the other hand, the outer layer of the formulation of Sano is impermeable to water as shown above and should not disappear for at least a few weeks because the outer layer should release a medicament for a long period of time in view of the fact that Sano's formulation is for intracorporeal implantation.

As such, the outer layers of Sano's formulation and Chen's formulation are quite different from each other in terms of their functions and materials. Accordingly, it is submitted to be meaningless or non-sensical to suggest that any motivation exists in the cited art to substitute the outer layer of Sano's formulation with the outer layer of Chen's formulation, to thereby allegedly arrive at a formulation of the present invention.

Consequently, because there is neither any suggestion nor motivation provided in the cited references, which would result in one skilled in the art combining the references' teachings in a fashion that might arguably arrive at the instant invention being claimed, it follows that the outstanding rejection over Chen and Sano cannot be sustained.

Additional Considerations

Sano's formulation has an end of the inner layer that is open to come into direct contact with the external environment, and therefore enables the release of a medicament immediately after the formulation is implanted intracorporeally (see, Figure 6). Accordingly, it is not necessary to substitute the outer layer of Sano's formulation with the outer layer of Chen's formulation to enable the release of a medicament for the first 30 minutes before the opening for extruding a medicament is formed. Moreover it is

submitted that there would be no motivation to do so without the disclosure of the present invention.

Accordingly, Applicants submit that the combination of references cited by the USPTO simply results from the application of an improper level of "hindsight reconstruction" as a standard for determining patentability under 35 USC § 103(a). This is improper. In this respect, it is submitted that the outstanding rejection relies upon teachings of Sano and Chen, which are inconsistent with each other and actually teach away from each other, in order to arrive at the present invention as claimed. As such, it is submitted that in no way is the present invention obvious to a person of ordinary skill in the art, and that such persons would never be able to arrive the present invention of a multiple layer pharmaceutical composition based upon the disclosures of Sano and Chen, whether such references are considered singularly or in combination.

CONCLUSION

Based on the remarks presented above, Applicants respectfully submit that each of claims 1-8 are now in condition for allowance. Issuance of a Notice of Allowance to this effect is thus warranted at present.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully

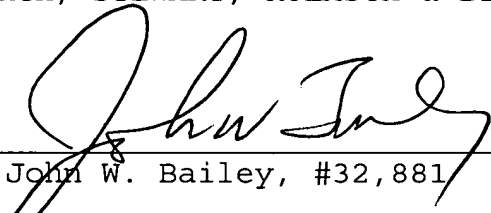
requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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By


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